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In vitro activity of three commercial bacteriophage cocktails against multidrug-resistant *Escherichia coli* and *Proteus* spp. strains of human and non-human origin

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Highlights

- Bacteriophages represent a therapeutic alternative against MDR Enterobacteriaceae.
- Three commercial phage cocktails were tested against 101 *E. coli* and *Proteus* spp. isolates.
- *E. coli* susceptibility to PYO, INTESTI and Septaphage was 61%, 67% and 9%, respectively.
- *Proteus* spp. susceptibility to PYO, INTESTI and Septaphage was 29%, 39% and 19%, respectively.
- New phages need to be integrated in such preparations to target more MDR pathogens.

ABSTRACT

Objectives: Bacteriophages may represent a therapeutic alternative to treat infections caused by multidrug-resistant (MDR) pathogens. However, studies analysing their activity against MDR Enterobacteriaceae are limited.

Methods: The in vitro lytic activity of three commercial bacteriophage cocktails (PYO, INTESTI and Septaphage) was evaluated against 70 *Escherichia coli* and 31 *Proteus* spp. of human and non-human origin. Isolates were characterised by phenotypic and genotypic methods and included 82 MDR strains [44 extended-spectrum-β-lactamase (ESBL)-producers (18 CTX-M-15-like, including ST131/ST648 *E. coli*); 27 plasmid-mediated AmpC β-lactamase (pAmpC)-producers (23 CMY-2-like, including ST131 *E. coli*); 3 ESBL + pAmpC-producers; and 8 carbapenemase-producers]. Phage susceptibility was determined by the spot test.

Results: *Escherichia coli* susceptibility to PYO, INTESTI and Septaphage was 61%, 67% and 9%, whereas that of *Proteus* spp. was 29%, 39% and 19%, respectively. For the subgroup of ESBL-producing *E. coli*/*Proteus* spp., the following susceptibility rates were recorded: PYO, 57%; INTESTI, 59%; and Septaphage, 11%. With regard to pAmpC-producers, 59%, 70% and 11% were susceptible to PYO, INTESTI and Septaphage, respectively. Five of eight carbapenemase-producers and three of four colistin-resistant *E. coli* were susceptible to PYO and INTESTI.

Conclusions: This is the first study analysing the activity of the above three cocktails against well-characterised MDR *E. coli* and *Proteus* spp. The overall narrow spectrum of activity observed could be related to the absence of specific bacteriophages targeting these contemporary MDR strains that are spreading in different settings. Therefore, bacteriophages targeting emerging MDR pathogens need to be isolated and integrated in such biopreparations.

Keywords:

Bacteriophage

Escherichia coli

Proteus spp.

ESBL

AmpC

Carbapenemase

1. Introduction

Treatment of infections caused by multidrug-resistant (MDR) Enterobacteriaceae represents a continuous challenge. These pathogens are frequently resistant to extended-spectrum cephalosporins owing to the production of extended-spectrum β-lactamases (ESBLs) and/or plasmid-mediated AmpC β-lactamases (pAmpCs) [1–3]. Moreover, even the last therapeutic options, namely carbapenems and polymyxins, are under attack due to the spread of carbapenemase- and/or MCR-1/2-producing strains, respectively [4,5].

In this overall scenario, the use of bacteriophages (highly species-specific self-propagating viruses that can infect and lyse bacteria) could represent a valid therapeutic alternative to treat infections caused by extended-spectrum cephalosporin- and/or carbapenem-resistant Gram-negative pathogens [6,7]. Bacteriophage therapy is part of the standard medical practice in the former Soviet Union countries. In contrast, in Western nations the use of phage therapy is unfamiliar and this has generated a lack of clinical studies analysing the efficacy of this possible alternative therapeutic approach [6,7]. Therefore, most of the available scientific literature in English presents data obtained only with animal models. For instance, bacteriophage treatment was effective in in vivo models with ESBL-producing *Escherichia coli*, including those belonging to the hyperepidemic clone of sequence type 131 (ST131) [8–10].

Whilst data regarding the in vitro activity of bacteriophages against *E. coli* and *Staphylococcus aureus* are available, studies analysing their activity against large

collections of MDR Enterobacteriaceae are very limited. Fitzgerald-Hughes et al. showed that 89% of human ESBL-producing *E. coli* isolates were susceptible to at least one of four bacteriophage cocktails [11]. However, strains were defined as ESBL-producers only using the phenotypic European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria; moreover, pAmpC- or carbapenemases-producers were not tested and multilocus sequence typing (MLST) was not performed to define the ST [11]. In another study, Sybesma et al. assessed the susceptibility of ESBL-producing *E. coli* and *Klebsiella pneumoniae* strains, all isolated from patients suffering from urinary tract infection (UTI), to four Georgian bacteriophage cocktails and several mono-phage preparations [12]. Their results showed great variability, with lytic activity ranging from 66% to 93% for *E. coli* and from 0% to 100% for *K. pneumoniae* [12]. Consistent results were also obtained by Gundogdu et al. who recently tested ESBL-producing *E. coli* from patients' blood and urine samples [13]. However, for these two latter studies, ESBL production was only phenotypically defined and no information on the ST or resistance gene profiles of the bacteria was presented [12,13].

To our knowledge, the activity of commercially available bacteriophage cocktails against well-defined MDR *E. coli* strains of animal and food origin has never been described. In the same context, data regarding *Proteus* spp. isolates detected in different settings are completely lacking. Therefore, in this work we aimed to assess the lytic effect of three commercial bacteriophage preparations, all available to the public in Georgia, on a large collection of well-characterised human and non-human *E. coli* and *Proteus* spp. strains.

2. Materials and methods

2.1. Bacteriophage cocktails

Three commercially available bacteriophage cocktails produced by Georgian institutions located in Tbilisi were tested. According to the manufacturers, they are all sterile-filtrate phage lysates of different bacterial species as listed below. The preparation lot numbers implemented during the present work are indicated in parentheses, along with the declared phage concentration specified by the provider.

2.1.1. PYO Bacteriophage

PYO Bacteriophage (lot # M1-801; Eliava BioPreparations, Tbilisi, Georgia) targets *E. coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Staphylococcus* spp. and *Streptococcus* spp. The specified concentration was $1 \times 10^{5–6}$ plaque-forming units (PFU)/mL.

2.1.2. INTESTI Bacteriophage

INTESTI Bacteriophage (lot # M2-801; Eliava BioPreparations) targets *E. coli*, *P. mirabilis*, *P. vulgaris*, *Salmonella* Paratyphi A and B, *Salmonella* Typhimurium, *Salmonella* Enteritidis, *Salmonella* Choleraesuis, *Salmonella* Oranienburg, *Shigella flexneri*, *Shigella sonnei*, *Shigella newcastle*, *P. aeruginosa*, *Staphylococcus* spp. and *Enterococcus* spp. The specified concentration was $1 \times 10^{5–6}$ PFU/mL.

2.1.3. Septaphage

Septaphage (lot # 01.05.15; Biochimpharm, Tbilisi, Georgia) targets different serogroups of enteropathogenic *E. coli*, *Proteus* spp., *S.* Paratyphi A and B, *S.* Typhimurium, *S.* Choleraesuis, *S.* Oranienburg, *S.* Enteritidis, *S. flexneri* (serogroups 1, 2, 3, 4 and 6), *S. sonnei*, *P. aeruginosa*, *Staphylococcus* spp. and *Enterococcus* spp. The specified concentration was 1×10^5 PFU/mL.

All three phage cocktails are available to the public without prescription in Georgia. In particular, PYO is used to treat purulent skin, surgical, oral, enteral and gynaecological infections, whereas INTESTI and Septaphage are implemented for intestinal infections.

2.2. Bacterial collection and characterisation

The in vitro activity of the above three phage preparations was evaluated against a collection of 70 well-characterised and contemporary *E. coli* isolates of human (*n* = 31), animal (*n* = 22) and food (*n* = 12) origin as well as 5 laboratory controls (Table 1). Overall, the majority of strains (43/70; 61%) were detected in the last 5 years (2015, *n* = 23; 2014, *n* = 2; 2013, *n* = 3; and 2012, *n* = 15). Most strains were previously characterised by phenotypic [minimum inhibitory concentration (MIC) determination using microdilution Trek panels] and genotypic [CheckPoints CT103 or CT103XL microarray, PCR/sequencing for *bla* genes, plasmid content by PCR-based replicon typing (PBRT) and MLST] methods [1,3,5,14–18]. In particular, the collection included 37 ESBL-producers (18 CTX-M-15-like), 21 pAmpC-producers (17 CMY-2-like), 2 ESBL + pAmpC-producers, and 7 carbapenemase-producers (4 NDM, 2 OXA-48 and 1 IMP). Four

colistin-resistant strains were also included, one of which carried the *mcr-1* resistance gene [5].

In addition, 21 well-characterised *P. mirabilis* of human (*n* = 18) and food (*n* = 3) origin [3] were tested, along with 10 *P. vulgaris* responsible for human bacteraemia at Bern University Hospital, University of Bern (Bern, Switzerland). Overall, 7 ESBL-producers (4 VEB, 2 TEM and one CTX-M), 6 pAmpC-producers (all CMY-2), 1 with CTX-M-9-/CMY-2-like and 1 carbapenemase (NDM)-producer were tested. Most strains (27/31, 87%) were detected in the last 5 years (2016, *n* = 9; 2015, *n* = 5; 2014, *n* = 6; 2013, *n* = 3; and 2012, *n* = 4) (Table 2).

Species identification of all *E. coli* and *Proteus* spp. strains was done using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Daltonics, Leipzig, Germany). Strains were defined as MDR according to Magiorakos et al. [19].

2.3. Susceptibility to bacteriophage cocktails

Phage susceptibility was determined by implementing the spot test with Double Agar Overlay Plaque Assay [20]. Briefly, a 10 μL loop of fresh overnight culture was grown for 2 h in 5 mL of brain–heart infusion (BHI) broth (Becton Dickinson, Allschwil, Switzerland) at 37 °C in a shaking incubator to reach mid-log bacterial phase. For each host bacteria, 100 μL of a 0.5 McFarland bacterial suspension was mixed in a BHI agarose matrix (‘top agar’, 0.6%), which was then distributed to solidify on a standard BHI agar plate (‘bottom

agar', 1.5%, dried for 2 h before use at room temperature). After drying, 10 μL of each of the four phage suspensions was spotted on the plate and was incubated overnight.

The next day, lysis zones (if any) were quantified using a common system assessing the success of phage infection [20]. In particular, strains showing confluent lysis (i.e. complete clearing: '++++'), semiconfluent lysis (i.e. clearing throughout but with faintly hazy background: '+++'), opaque lysis (i.e. turbidity throughout the cleared zone: '++') or 'tâches vièrges' (i.e. individual clear or opaque plaques: '+') were defined as susceptible to the phage compounds tested. Strains showing no activity (i.e. no clearing: 'R') were defined as resistant.

All of the susceptibility tests were performed at the Institute for Infectious Diseases of the University of Bern between 29 August 2016 and 6 October 2016 by two of the authors (OJB and RT). The spot test was performed two times on different days, using vials belonging to different boxes (except for PYO, for which two vials of the same box were tested) and BHI broth/agar plates prepared in different sessions. Results were interpreted by at least three operators and showed consistency for all tested strains, with no difference greater than one '+' between the two experiments (with very few exceptions, for which a third assay was performed).

3. Results and discussion

3.1. Escherichia coli strains

As shown in Table 3, the overall susceptibility of *E. coli* strains to PYO, INTESTI and Septaphage was 61.4% (including 7/70 with '+++' and 6/70 with '++++'), 67.1% (including 9/70 with '+++' and 5/70 with '++++') and 8.6% (including 4/70 with '++++'), respectively. In particular, PYO cocktail showed lytic activity against 67.7% (21/31), 50.0% (11/12) and 66.7% (8/12) of human, animal and food strains, whereas the activities for INTESTI were 64.5% (20/31), 63.6% (14/22) and 75.0% (9/12), respectively (Table 1).

For the overall subgroup of the ESBL-producing *E. coli* strains (*n* = 37), the following susceptible rates were recorded: PYO, 54.0%; INTESTI, 56.7%; and Septaphage, 2.7% (Table 3). In the study by Fitzgerald-Hughes et al., 100 phenotypically defined ESBL-producing *E. coli* were susceptible to PYO and INTESTI in 36% and 54% of cases, respectively [11]. Septaphage was not tested, but the authors indicated that two additional phage cocktails, not tested in the present study, were much more active (i.e. SES and ENKO, at 87% and 89%, respectively) [11]. In another analysis testing only nine ESBL-producing *E. coli* strains, Sybesma et al. obtained the following susceptibility rates: PYO, 78%; and INTESTI, SES and ENKO, all 89% [12].

With regard to the pAmpC-producing *E. coli* strains (*n* = 21), 71.4% and 85.7% were susceptible to PYO and INTESTI, respectively, whereas only 14.3% were susceptible to Septaphage. Moreover, five of seven carbapenemase-producers and three of four colistin-resistant strains (including the MCR-1-producer) were susceptible to PYO and

INTESTI, respectively (Tables 1 and 3). We highlight that no previous studies have analysed the lytic activity of commercial bacteriophage cocktails against this specific group of MDR *E. coli* strains. Data regarding the life-threatening carbapenem- and colistin-resistant strains were promising [4,5,21] but should be confirmed testing a larger collection of strains.

In this study, five of seven *E. coli* strains belonging to the hyperepidemic clones ST131 and ST648 [22] were susceptible both to PYO and INTESTI (Tables 1 and 3). We also emphasise that the activity of the phage compounds was relatively different even though the *E. coli* strains belonged to the same STs (e.g. see the results of the five ST131 and four ST420 strains in Table 1). These differences probably depend on the fact that some bacterial clones may acquire and develop different escape strategies (e.g. inhibition of CRISPR-Cas or phage adsorption systems) against bacteriophages [23]. Therefore, as recently explored for *S.* Typhimurium [24], further studies with a larger collection of hyperepidemic *E. coli* clones coupled with whole-genome sequence analyses should be performed to clarify the underlying molecular mechanisms that make each unique bacteria resistant to phage attack.

3.2. Proteus spp. strains

As anticipated, published data regarding the activity of commercial bacteriophage cocktails against *Proteus* spp. strains are lacking. In the present study, the overall susceptibility of *Proteus* spp. to PYO, INTESTI and Septaphage was 29.0% (including 3/31 with '+++' or '++++'), 38.7% (including 4/31 with '+++' or '++++') and 19.3% (including

5/31 with '+++' or '++++'), respectively (Table 2 and 3). In particular, the following susceptibility rates were recorded for *P. mirabilis* and *P. vulgaris*, respectively: PYO, 33.3% and 20.0%; INTESTI, 47.6% and 20.0%, and Septaphage, 28.6% and 0%. With regard to the MDR *P. mirabilis* strains (*n* = 15), 40.0% were susceptible both to PYO and INTESTI, whereas only 26.7% were susceptible to Septaphage (Table 3). Owing to the relatively small number of tested strains, larger collections of MDR *Proteus* spp. should be tested to confirm these results.

3.3. Overall strains

Surprisingly, Septaphage displayed an almost complete lack of activity both against *E. coli* and *Proteus* spp. strains. Moreover, a noteworthy variability between the two preparations expected to target the same bacterial species (i.e. INTESTI and Septaphage) could be noted (Table 3). This may be linked to the different content in terms of strains-specific bacteriophages with lytic activity. However, to our knowledge, only the INTESTI preparation has been well characterised using metagenomic analyses [25]. Alternatively, the reason for such remarkable divergences among the phage compounds could rely on different production methods [26], leading to insufficient viral titre of the final biopreparation. In this context, we note that a concentration of $10^{5–6}$ PFU/mL is indicated both for INTESTI and PYO, whereas the concentration is 10^5 PFU/mL for Septaphage.

The overall narrow spectrum of activity of the cocktails observed against the MDR *E. coli* and *Proteus* spp. analysed in this study could be related to the absence of specific bacteriophages targeting these contemporary strains that are usually responsible for

human infections both in hospital and community settings [17,22,27–29]. Besides, it is remarkable that most of the fully antibiotic-sensitive *P. mirabilis* and *P. vulgaris* strains (10/16; 62.5%) were shown to be completely resistant to the bacteriophage cocktails with declared activity against such species.

Therefore, the spectrum of activity of the above cocktails should be expanded integrating new lytic phages. We note for instance that Dufour et al. have recently selected a bacteriophage (LM33_P1) with lytic activity against ca. 65% of ST131 *E. coli* isolates tested and also able to significantly reduce the organ bacterial load in pneumonia, septicaemia and UTI in in vivo models [9]. Pouillot et al. isolated another bacteriophage ($EC200^{PP}$) specific for *E. coli* ST131: although no data regarding its spectrum of activity against a collection of ST131 strains was provided, this phage demonstrated potent activity in sepsis and meningitis in vivo models [10].

A limited number of bacteriophages infecting *Proteus* spp. have so far been selected and studied [30,31]. Nevertheless, we underline that Melo et al. have recently isolated and characterised a novel bacteriophage (Pm5461) that was able to target all 26 *Proteus* spp. tested in the study. Unfortunately, the antimicrobial susceptibility phenotype of the strains and their year of collection were not defined [32].

Finally, we should note that the spot test can lead to an overestimation of positive results as a consequence of the ‘lysis-from-without’ phenomenon [33]. We are therefore aware

that the results of the current study might partially overestimate the susceptibility results for PYO and INTESTI compounds.

4. Conclusions

Escherichia coli and *Proteus* spp. are frequently responsible for UTIs and bacteraemia [27,34]. Furthermore, difficult-to-treat infections due to MDR *E. coli* and *Proteus* spp. are increasing worldwide, leading to higher morbidity and mortality rates [1,28,29,35]. We also note that such MDR pathogens can cause intestinal colonisation of humans [5,16] and animals [2,14,18,21], along with contamination of the food chain [3,36,37]. Since exchange of MDR strains among these settings has been demonstrated [2,18], this overall phenomenon, also known as the 'One-Health concept', contributes enormously to the expansion and spread of MDR Enterobacteriaceae [38].

In this scenario, we therefore explored the use of bacteriophages as a possible alternative to antibiotics. In particular, we assessed for the first time the in vitro susceptibility of a large collection of well-characterised *E. coli* and *Proteus* spp. to three commercial bacteriophage cocktails. This information is essential to understand whether these phage compounds can be hypothetically implemented in large scale to treat infections (e.g. UTIs) [6,7], to decolonise intestinal carriers and/or to decontaminate food stuffs [39] from current MDR *E. coli* and *Proteus* spp.

As a result of the analysis, we observed neither strong lysis ('+++' to '++++') for the majority of the tested strains, nor a wide spectrum of activity against the total number of

bacteria, especially regarding *Proteus* spp. The most active compound (INTESTI) showed ca. 70% and 40% activity against *E. coli* and *Proteus* spp., respectively (although only 15–20% with activity ≥ '+++').

The great diversity of currently circulating MDR *E. coli* and *Proteus* spp. is partially exemplified by the bacterial collection studied here. The tested cocktails contained only a few bacterial viruses targeting such contemporary pathogens. Therefore, new bacteriophages active against emerging MDR strains need to be isolated and integrated in such biopreparations. Only in this way will phage libraries start to reflect the worldwide and actual situation of MDR and pandemic isolates [22]. Moreover, the newly isolated bacteriophages should also be well characterised [9,10,25,32] and should be produced according to Good Manufacturing Practice (GMP) standards in order to become, at a later stage, approved for clinical therapy [7,26].

To become a real alternative to standard antimicrobials, phage cocktails first need to be brought up to date in terms of clinically relevant strain-specific viral content [40]. Only then will the progress towards therapeutic use of bacteriophages for the management of difficult-to-treat infections caused by MDR organisms meet a ground to grow and flourish also in the Western world.

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Table 1

Characteristics of 70 multidrug-resistant *Escherichia coli* strains and their susceptibility to four commercial bacteriophage cocktails

Strain ID	Origin (source; year of isolation)	Main *bla* genes	ST [a]	Susceptibility according to EUCAST [b]					Bacteriophage susceptibility [c]		
				CTX	IPM	CIP	GEN	COL	PYO	INTESTI	Septaphage
4811.56	Human (vaginal; 2011)	CTX-M-15	ST131	R	S	S	S	S	R	R	R
4901.28	Human (urine; 2011)	CTX-M-15	ST131	R	S	R	R	S	+++	+++	R
LA12095038/Ec-38	Human (urine; 2012)	CTX-M-15	ST131	R	S	R	R	S	+++	+++	R
4809.08	Human (liver abscess; 2011)	CTX-M-15	ST648	R	S	R	R	S	R	R	R
8-R MAC III	Human (stool; 2015)	CTX-M-15	ST648	R	S	R	R	S	++	++	R
MSA971	Poultry (cloacal; 2010–2011)	CTX-M-15	*ST533*	R	S	I	R	S	R	+	R

83-R MAC III	Human (stool; 2015)	CTX-M-15	ST394	R	S	S	S	S	R	R	R
97R DrigI	Human (stool; 2015)	CTX-M-15	ST291	R	S	S	S	S	+	R	R
23-R DrigII	Human (stool; 2015)	CTX-M-15	ST200	S	S	S	S	S	+	+	R
8-R MAC I	Human (stool; 2015)	CTX-M-15	ST245	R	S	R	R	S	+	+	R
73-R chromB	Human (stool; 2015)	CTX-M-15	ST412	R	S	S	S	S	++	+	R
IMD0077/11	Cattle (stool; 2010–2011)	CTX-M-15	*ST537*	R	S	R	S	S	R	R	R
Sidava	Cat (stool; 2015)	CTX-M-15	ST73	R	S	S	S	S	R	+	R
68-M3 SupI	Human (stool; 2015)	CTX-M-15-like	ST48	R	S	S	S	S	R	R	R
97-R DrigII	Human (stool; 2015)	CTX-M-15-like	ST841	R	S	S	S	S	R	+	R

29-R MacIII	Human (stool; 2015)	CTX-M-15-like	ST349	R	S	S	S	S	+	R	R
43-R Drig	Human (stool; 2015)	CTX-M-15-like	ST617	R	S	R	S	S	R	R	R
56-M3-Ec-Col-R	Human (stool; 2015)	CTX-M-15-like	ST630	R	S	R	S	R	+++	++++	R
Ylraz I	Dog (stool; 2013)	CTX-M-1	ST949	R	S	S	S	S	R	R	R
IMD0041/11	Swine (stool; 2010–2011)	CTX-M-1	*ST529*	R	S	I	S	S	++	+	R
5A	Chicken meat (2012)	CTX-M-1	ST248	R	S	S	S	S	R	R	R
7A	Chicken meat (2012)	CTX-M-1	ST114	R	S	S	S	S	+	+	R
7B	Chicken meat (2012)	CTX-M-1	na	R	S	S	S	S	+++	++++	0
11A	Chicken meat (2012)	CTX-M-1	ST130	R	S	S	S	S	+	+	R

9A	Chicken meat (2012)	CTX-M-1	ST602	R	S	S	S	S	+	+	R
18A	Chicken meat (2012)	CTX-M-1	ST23	R	S	S	S	S	+	+++	R
20C	Chicken meat (2012)	CTX-M-1	na	R	S	S	S	S	++	+	R
100-R-ChromII	Human (stool; 2015)	CTX-M group 1	na	R	S	S	S	S	R	R	R
100-R-Drig	Human (stool; 2015)	CTX-M group 1	ST155	R	S	S	S	S	+	+	++++
Socra	Dog (stool; 2015)	CTX-M-14	ST162	R	S	S	R	S	R	R	R
11/IMD0477	Poultry (cloacal; 2010–2011)	TEM-52	*ST524*	I	S	I	S	S	+	+	R
IMD 0050/11	Poultry (cloacal; 2010-11)	TEM-52	*ST86*	R	S	S	S	S	R	R	R
4A	Chicken meat (2012)	TEM-52	ST23	R	S	S	S	S	+	+	R

100-R-Ec	Human (stool; 2015)	TEM-1 (*mcr-1*-positive)	ST10	S	S	R	S	R	+	+	R
MSA899	Poultry (cloacal; 2010–2011)	SHV-12	*ST21*	I	S	I	S	S	R	R	R
3A	Chicken meat (2012)	SHV-12	ST155	R	S	S	S	S	R	R	R
15A	Chicken meat (2012)	SHV-12	ST155	R	S	S	S	S	R	R	R
2390300	Human (wound; 2015)	CMY-2	ST131	I	S	S	S	S	+	+	R
2402500	Human (respiratory; 2015)	CMY-33	ST131	R	S	S	S	S	++	+++	R
MSA1088	Poultry (cloacal; 2010–2011)	CMY-2	ST38	R	S	I	S	S	+	+	R
MSA970	Poultry (cloacal; 2010–2011)	CMY-2	ST420	R	S	I	S	S	+++	+++	R

MSA972	Poultry (cloacal; 2010–2011)	CMY-2	ST420	R	S	I	S	S	++++	+++	+
MSA992	Poultry (cloacal; 2010–2011)	CMY-2	ST420	R	S	I	S	S	+++	++++	R
11/IMD0087	Poultry (cloacal; 2010–2011)	CMY-2	ST420	R	S	I	S	S	++++	++++	R
MSA991	Poultry (cloacal; 2010–2011)	CMY-2	*ST539*	R	S	I	S	S	+	+	R
MSA935	Swine (nose; 2010–2011)	CMY-2	*ST539*	R	S	S	S	S	+	+	R
11/IMD0129	Poultry (cloacal; 2010–2011)	CMY-2	*ST9*	R	S	I	S	S	+	+	R
11/IMD0147	Poultry (cloacal; 2010–2011)	CMY-2	*ST527*	R	S	I	S	S	+	+	R
Sinaj	Cat (stool; 2015)	CMY-2	ST56	R	S	S	S	S	R	+	R

MSA967	Swine (nose; 2010–2011)	CMY-2	*ST2*	R	S	R	S	S	R	R	R
MSA969	Swine (nose; 2010–2011)	CMY-2	*ST532*	R	S	I	S	S	R	R	R
MSA909	Poultry (cloacal; 2010–2011)	CMY-2-like	na	R	S	S	S	S	R	R	R
1C	Turkey meat (2012)	CMY-2	ST117	R	S	S	S	S	+	++	R
13C	Chicken meat (2012)	CMY-2	ST38	R	S	S	S	S	R	+	R
2081272	Human (blood; 2012)	DHA	na	S	S	R	S	S	+	++	+
73-R Mac	Human (stool; 2015)	DHA	ST10	S	S	S	S	S	+++	+++	R
GC 2919	Laboratory strain	ACT-1	na	R	S	S	S	S	+++	+++	++++
AH3966	Laboratory strain	FOX	na	S	S	S	S	S	R	+	R

2152061	Human (urine; 2013)	CTX-M-15-/CMY-2-like	na	R	S	R	S	S	R	R	R
804133/14	Human (stool; 2014)	CTX-M-15, CMY-2	ST117	R	S	S	R	S	+	+	R
01C60-LF	Human (stool; 2013)	OXA-48, CTX-M-9	na	R	S	R	R	S	+++	++	R
2265478	Human (urine; 2014)	OXA-48	na	S	S	S	R	S	++	+	R
2058665	Human (na; 2012)	NDM-1-/CMY-2-like	na	R	R	R	R	S	+	++	R
AC-IT-1	Human (urine; 2010)	NDM-1, CTX-M-15	ST101	R	R	R	R	S	+++	++++	++++

2411192	Human (stool; 2015)	NDM-1-/CMY-2-like	na	R	R	R	S	S	R	R	R
ATCC BAA-2452	Laboratory strain	NDM-1	na	R	R	S	R	S	R	R	R
DH10B	Laboratory strain	IMP-1	na	R	R	S	S	S	+++	+++	++++
18-M3-Ec-Col-R	Human (stool; 2015)	– [d]	ST141	S	S	S	S	R	+	++	R
26-Ec-Col-R	Human (stool; 2015)	–	ST69	S	S	S	S	R	R	R	R
ATCC 35218	Laboratory strain	–	na	S	S	S	S	S	+	+	R

ST, sequence type; CTX, cefotaxime; IPM, imipenem; CIP, ciprofloxacin; GEN, gentamicin; COL, colistin, R, resistant; I, intermediate; S, susceptible; na, not available.

[a] Most STs were obtained with the Warwick scheme (http://enterobase.warwick.ac.uk/species/index/ecoli); those indicated in italic were obtained with the Pasteur scheme (http://bigsdb.web.pasteur.fr/).

[b] European Committee on Antimicrobial Susceptibility Testing (EUCAST) v.6.0.

[c] Strains were defined as susceptible to the bacteriophages when confluent lysis (i.e. complete clearing: '++++'), semiconfluent lysis (i.e. clearing throughout but with faintly

hazy background: '+++'), opaque lysis (i.e. turbidity throughout the cleared zone: '++') or 'tâches vièrges' (i.e. a few individual clear or opaque plaques: '+') was recorded. Strains showing no activity (i.e. no clearing: 'R') were defined as resistant.

[d] – Indicates no *bla* genes conferring resistance to extended-spectrum cephalosporins.

Table 2

Characteristics of the 21 *Proteus mirabilis* and 10 *Proteus vulgaris* strains and their susceptibility to three commercial bacteriophage cocktails

Strain ID	Species	Origin (source; year of isolation)	Main *bla* genes	Susceptibility according to EUCAST [a]				Bacteriophage susceptibility [b]		
				CTX	IPM	CIP	GEN	PYO	INTESTI	Septphage
VB1248	*P. mirabilis*	Human (blood; 2009)	VEB-6	R	S	R	R	+	+	+++
16B	*P. mirabilis*	Turkey meat (2012)	VEB-6	R	S	R	R	++	+++	++++
17B	*P. mirabilis*	Turkey meat (2012)	VEB-6	R	S	R	R	++	++	++++
5705.10	*P. mirabilis*	Human (urine; 2015)	VEB-1-like	R	S	R	I	+++	+++	+++
1409101274	*P. mirabilis*	Human (na; 2014)	CTX-M-9-like	R	S	na	na	++	++	R
5304.28	*P. mirabilis*	Human (urine; 2013)	TEM-3-like	R	S	R	R	R	R	R
5809.58	*P. mirabilis*	Human (abscess; 2015)	TEM-3-like	R	S	R	R	R	R	R

Strain ID	Species	Origin (source; year of isolation)	Main *bla* genes	Susceptibility according to EUCAST [a]				Bacteriophage susceptibility [b]		
				CTX	IPM	CIP	GEN	PYO	INTESTI	Septaphage
4810.05	*P. mirabilis*	Human (urine; 2011)	CMY-2	R	S	I	S	R	R	R
4810.40	*P. mirabilis*	Human (blood; 2011)	CMY-2	R	S	R	S	R	R	R
4812.18	*P. mirabilis*	Human (urine; 2011)	CMY-2	R	S	R	S	R	R	R
5106.42	*P. mirabilis*	Human (wound; 2012)	CMY-2	R	S	R	S	R	R	R
804133-Nr.6	*P. mirabilis*	Human (na; 2014)	CMY-2-like	R	S	R	R	+++	+++	R
15D	*P. mirabilis*	Chicken meat (2012)	CMY-2	I	S	S	S	R	R	R
5909.63	*P. mirabilis*	Human (urine; 2015)	CTX-M-9-/CMY-2-like	R	S	I	R	R	R	R

Strain ID	Species	Origin (source; year of isolation)	Main *bla* genes	Susceptibility according to EUCAST [a]				Bacteriophage susceptibility [b]		
				CTX	IPM	CIP	GEN	PYO	INTESTI	Septaphage
6012.36	*P. mirabilis*	Human (stool; 2016)	NDM-1-/CMY-2-like	R	R	R	R	R	R	R
6012.61	*P. mirabilis*	Human (blood; 2016)	– [c]	S	S	S	S	R	++	+
6012.72	*P. mirabilis*	Human (blood; 2016)	–	S	S	S	S	R	R	R
6103.33	*P. mirabilis*	Human (blood; 2016)	–	S	S	S	S	R	+	R
6107.51	*P. mirabilis*	Human (blood; 2016)	–	S	S	S	S	R	R	R
6202.32	*P. mirabilis*	Human (blood; 2016)	–	S	S	S	S	+++	++++	+++
6204.01	*P. mirabilis*	Human (blood; 2016)	–	S	S	S	S	R	+	R
5307.35	*P. vulgaris*	Human (blood; 2013)	–	S	S	S	S	R	R	R

Strain ID	Species	Origin (source; year of isolation)	Main *bla* genes	Susceptibility according to EUCAST [a]				Bacteriophage susceptibility [b]		
				CTX	IPM	CIP	GEN	PYO	INTESTI	Septphage
5307.79	*P. vulgaris*	Human (blood; 2013)	–	S	S	S	S	R	R	R
5408.26	*P. vulgaris*	Human (blood; 2014)	–	S	S	S	S	R	R	R
5410.37	*P. vulgaris*	Human (blood; 2014)	–	S	S	S	S	R	R	R
5502.26	*P. vulgaris*	Human (blood; 2014)	–	S	S	S	S	R	R	R
5507.56	*P. vulgaris*	Human (blood; 2014)	–	S	S	S	S	R	R	R
5801.02	*P. vulgaris*	Human (blood; 2015)	–	S	S	S	S	R	R	R
5906.65	*P. vulgaris*	Human (blood; 2015)	–	S	S	S	S	R	R	R
6202.78	*P. vulgaris*	Human (urine; 2016)	–	S	S	S	S	++	++	R

Strain ID	Species	Origin (source; year of isolation)	Main *bla* genes	Susceptibility according to EUCAST [a]				Bacteriophage susceptibility [b]		
				CTX	IPM	CIP	GEN	PYO	INTESTI	Septphage
6208.26	*P. vulgaris*	Human (blood; 2016)	–	S	S	S	S	+	+	R

CTX, cefotaxime; IPM, imipenem; CIP, ciprofloxacin; GEN, gentamicin; R, resistant; I, intermediate; S, susceptible; na, not available.

Proteus spp. is naturally resistant to colistin.

[a] European Committee on Antimicrobial Susceptibility Testing (EUCAST) v.6.0.

[b] Strains were defined as susceptible to the bacteriophages when confluent lysis (i.e. complete clearing: '++++'), semiconfluent lysis (i.e. clearing throughout but with faintly hazy background: '+++'), opaque lysis (i.e. turbidity throughout the cleared zone: '++') and 'tâches vièrges" (i.e. a few individual clear or opaque plaques: '+') was recorded. Strains showing no activity (i.e. no clearing: 'R') were defined as resistant.

[c] – Indicates no *bla* genes conferring resistance to extended-spectrum cephalosporins.

Table 3

Summary of the susceptibility of the *Escherichia coli* and *Proteus* spp. strains to three commercial bacteriophage cocktails

Phage cocktail/strain group	Results of the spot test (%) [a]				
	R	+	++	+++	++++
PYO Bacteriophage (Eliava)					
Overall strains (*n* = 101)	48.5	25.7	9.9	9.9	5.9
E. coli (*n* = 70)	38.6	34.3	8.6	10.0	8.6
Only ESBLs (*n* = 37)	45.9	32.4	10.8	5.4	5.4
Only pAmpCs (*n* = 21)	28.6	38.1	4.7	9.5	19.0
Carbapenemases (*n* = 7)	28.6	14.3	14.3	42.8	0
ST131 or ST648 (*n* = 7)	28.6	14.3	28.6	14.3	14.3
Proteus spp. (overall, *n* = 31)	70.9	6.4	12.9	9.7	0
Proteus mirabilis (*n* = 21)	66.7	4.7	14.3	14.3	0
MDR (*n* = 15) [b]	60.0	6.7	20.0	13.3	0
Proteus vulgaris (*n* = 10)	80.0	10.0	10.0	0	0
INTESTI Bacteriophage (Eliava)					
Overall strains (*n* = 101)	41.6	30.7	9.9	11.8	5.9
E. coli (*n* = 70)	32.8	38.6	8.6	12.8	7.1
Only ESBLs (*n* = 37)	43.2	40.5	2.7	8.1	5.4
Only pAmpCs (*n* = 21)	14.3	42.8	9.5	23.8	9.5
Carbapenemases (*n* = 7)	28.6	14.3	28.6	14.3	14.3
ST131 or ST648 (*n* = 7)	28.6	14.3	14.3	42.8	0
Proteus spp. (overall, *n* = 31)	61.3	12.9	12.9	9.7	3.2
P. mirabilis (*n* = 21)	52.4	14.3	14.3	14.3	4.7
MDR (*n* = 15) [b]	60.0	6.7	13.3	20.0	0
P. vulgaris (*n* = 10)	80.0	10.0	10.0	0	0
Septaphage (Biochimpharm)					
Overall strains (*n* = 101)	88.1	2.9	0	2.9	5.9
E. coli (*n* = 70)	91.4	2.8	0	0	5.7

Only ESBLs (*n* = 37)	97.3	0	0	0	2.7
Only pAmpCs (*n* = 21)	85.7	9.5	0	0	4.7
Carbapenemases (*n* = 7)	71.4	0	0	0	28.6
ST131 or ST648 (*n* = 7)	100	0	0	0	0
Proteus spp. (overall, *n* = 31)	80.6	3.2	0	9.7	6.4
P. mirabilis (*n* = 21)	71.4	4.7	0	14.3	9.5
MDR (*n* = 15) [b]	73.3	0	0	13.3	13.3
P. vulgaris (*n* = 10)	100	0	0	0	0

ESBL, extended-spectrum β-lactamase; pAmpC, plasmid-mediated AmpC β-lactamase; MDR, multidrug-resistant.

[a] Strains were defined as susceptible to the bacteriophages when confluent lysis (i.e. complete clearing: '++++'), semiconfluent lysis (i.e. clearing throughout but with faintly hazy background: '+++'), opaque lysis (i.e. turbidity throughout the cleared zone: '++') or 'tâches vièrges' (i.e. a few individual clear or opaque plaques: '+') was recorded. Strains showing no activity (i.e. no clearing: 'R') were defined as resistant.

[b] Including 7 ESBL-producers, 6 pAmpC-producers, 1 with CTX-M-9-/CMY-2-like and 1 carbapenemase (NDM)-producer.